ITRACONAZOLE- itraconazole capsule
Accord Healthcare Inc.

Itraconazole Capsules

Rx only

BOXED WARNING

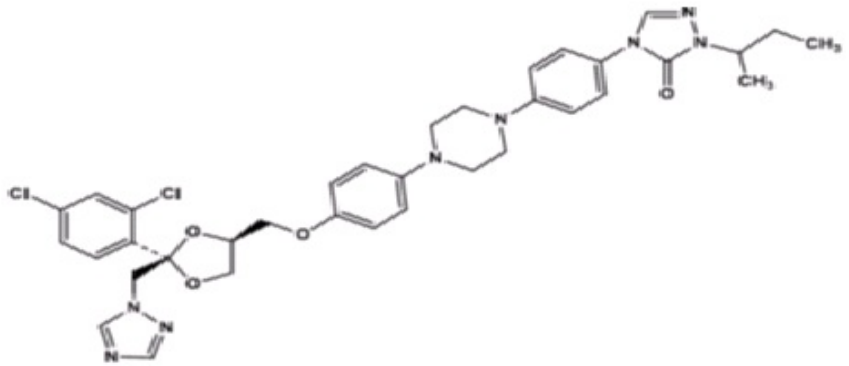
Congestive Heart Failure, Cardiac Effects and Drug Interactions:

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. If signs or symptoms of congestive heart failure occur during administration of itraconazole capsules, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations for more information.)

Drug Interactions: Coadministration of the following drugs are contraindicated with Itraconazole Capsules: methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazole, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor. In addition, coadministration with colchicine, fesoterodine and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment, and coadministration with eliglustat is contraindicated in subjects that are poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors. See PRECAUTIONS: Drug Interactions Section for specific examples. Coadministration with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. See CONTRAINDICATIONS and WARNINGS Sections, and PRECAUTIONS: Drug Interactions Section for specific examples.

DESCRIPTION

Itraconazole is an azole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:



(±)-1-[(R*)- sec-butyl]-4-[p-[4-[p-[[(2 R*,4 S*)-2-(2,4-dichlorophenyl)-2-(1 H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ ^{2}-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)- sec-butyl]-4-[p-[4-[p-[[(2 S*,4 R*)-2-(2,4-dichlorophenyl)-2-(1 H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ ^{2}-1,2,4-triazolin-5-one

or

(±)-1-[(RS)- sec-butyl]-4-[p-[4-[p-[[(2 R,4 S)-2-(2,4-dichlorophenyl)-2-(1 H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ ^{2}-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

Itraconazole capsules contain 100 mg of itraconazole coated on sugar spheres. Inactive ingredients are hard gelatin capsule, hypromellose, polyglykol (PEG 20,000), purified talc, and sugar spheres (maize starch and sucrose). Components of the gelatin capsule include FD&C Blue No. 1, FD&C Blue No. 2, gelatin, D&C Red No. 28, and titanium dioxide. The printing ink contains potassium hydroxide, propylene glycol, shellac, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism:

General Pharmacokinetic Characteristics

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with C_{max} values of 0.5 µg/ml, 1.1 µg/ml and 2.0 µg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following an oral capsule dose. The observed absolute oral bioavailability of itraconazole is about 55%.

The oral bioavailability of itraconazole is maximal when itraconazole capsules are taken immediately after a full meal. Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H_2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases. (See PRECAUTIONS: Drug Interactions.) Absorption of itraconazole under fasted conditions in these subjects is increased when itraconazole capsules are administered with an acidic beverage (such as a

non-diet cola). When itraconazole capsules were administered as a single 200-mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H_2-receptor antagonist, itraconazole absorption was comparable to that observed when itraconazole capsules were administered alone. (See PRECAUTIONS: Drug Interactions.)

Itraconazole exposure is lower with the Capsule formulation than with the Oral Solution when the same dose of drug is given. (See WARNINGS)

Distribution

Most of the itraconazole in plasma is bound to protein (99.8%), with albumin being the main binding component (99.6% for the hydroxy-metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (>700 L), suggesting extensive distribution into tissues. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma.

Metabolism

Itraconazole is extensively metabolized by the liver into a large number of metabolites. *In vitro* studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole; trough plasma concentrations of this metabolite are about twice those of itraconazole.

Excretion

Itraconazole is excreted mainly as inactive metabolites in urine (35%) and in feces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabeled dose, fecal excretion of unchanged drug ranges from 3% to 18% of the dose.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4-week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment – for at least six months after the end of a 3-month treatment period.

Special Populations:

Renal Impairment:

Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200-mg oral dose of itraconazole was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 mL/min. × 1.73 m^2, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and $AUC_{0–8h}$). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups. After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50 to 79 ml/min), moderate (defined in this study as CrCl 20 to 49 ml/min), and severe renal impairment (defined in this study as CrCl <20 ml/min) were similar to that in healthy subjects (range of means 42 to 49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively). Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function. Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Hepatic Impairment:

Itraconazole is predominantly metabolized in the liver. A pharmacokinetic study was conducted in 6 healthy and 12 cirrhotic subjects who were administered a single 100-mg dose of itraconazole as

capsule. A statistically significant reduction in mean C_{max} (47%) and a twofold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC, was similar in cirrhotic patients and in healthy subjects. Data are not available in cirrhotic patients during long-term use of itraconazole. (See CONTRAINDICATIONS, PRECAUTIONS: Drug Interactions and DOSAGE AND ADMINISTRATION.)

Decreased Cardiac Contractility:

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole intravenous infusion, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of itraconazole capsules, itraconazole should be discontinued. (See BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

MICROBIOLOGY

Mechanism of Action:

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity In Vitro and in Clinical Infections:

Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, and Trichophyton* species (See INDICATIONS AND USAGE, Description of Clinical Studies).

Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

Drug Resistance:

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

Itraconazole is not active against *Zygomycetes* (e.g., *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

Cross-resistance:

Several *in vitro* studies have reported that some fungal clinical isolates with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed.

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi.

Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

INDICATIONS AND USAGE

Itraconazole capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Blastomycosis, pulmonary and extrapulmonary
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained before therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, antiinfective therapy should be adjusted accordingly.

Itraconazole capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

- Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium), and
- Onychomycosis of the fingernail due to dermatophytes (tinea unguium).

Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Description of Clinical Studies:

Blastomycosis:

Analyses were conducted on data from two open-label, non-concurrently controlled studies (N=73 combined) in patients with normal or abnormal immune status. The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first 2 weeks, and all signs and symptoms cleared between 3 and 6 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole for the treatment of blastomycosis compared with the natural history of untreated cases.

Histoplasmosis:

Analyses were conducted on data from two open-label, non-concurrently controlled studies (N=34 combined) in patients with normal or abnormal immune status (not including HIV-infected patients). The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first 2 weeks, and all signs and symptoms cleared between 3 and 12 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole for the treatment of histoplasmosis, compared with the natural history of untreated cases.

Histoplasmosis in HIV-infected patients:

Data from a small number of HIV-infected patients suggested that the response rate of histoplasmosis in HIV-infected patients is similar to that of non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse.

Aspergillosis:

Analyses were conducted on data from an open-label, "single-patient-use" protocol designed to make itraconazole available in the U.S. for patients who either failed or were intolerant of amphotericin B therapy (N=190). The findings were corroborated by two smaller open-label studies (N=31 combined) in the same patient population. Most adult patients were treated with a daily dose of 200 to 400 mg, with a median duration of 3 months. Results of these studies demonstrated substantial evidence of effectiveness of itraconazole as a second-line therapy for the treatment of aspergillosis compared with the natural history of the disease in patients who either failed or were intolerant of amphotericin B therapy.

Onychomycosis of the toenail:

Analyses were conducted on data from three double-blind, placebo-controlled studies (N=214 total; 110 given itraconazole capsules) in which patients with onychomycosis of the toenails received 200 mg of itraconazole capsules once daily for 12 consecutive weeks. Results of these studies demonstrated mycologic cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 54% of patients. Thirty-five percent (35%) of patients were considered an overall success (mycologic cure plus clear or minimal nail involvement with significantly decreased signs) and 14% of patients demonstrated mycologic cure plus clinical cure (clearance of all signs, with or without residual nail

deformity). The mean time to overall success was approximately 10 months. Twenty-one percent (21%) of the overall success group had a relapse (worsening of the global score or conversion of KOH or culture from negative to positive).

Onychomycosis of the fingernail:

Analyses were conducted on data from a double-blind, placebo-controlled study (N=73 total; 37 given itraconazole capsules) in which patients with onychomycosis of the fingernails received a 1-week course of 200 mg of itraconazole capsules b.i.d., followed by a 3-week period without itraconazole, which was followed by a second 1-week course of 200 mg of itraconazole capsules b.i.d. Results demonstrated mycologic cure in 61% of patients. Fifty-six percent (56%) of patients were considered an overall success and 47% of patients demonstrated mycologic cure plus clinical cure. The mean time to overall success was approximately 5 months. None of the patients who achieved overall success relapsed.

CONTRAINDICATIONS

Congestive Heart Failure:

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. (See BOXED WARNING, WARNINGS, PRECAUTIONS: Drug Interactions-Calcium Channel Blockers, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations.)

Drug Interactions:

Coadministration of a number of CYP3A4 substrates are contraindicated with Itraconazole. Plasma concentrations increase for the following drugs: levaceytlmethadol (levomethadyl), methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazole, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor. In addition, coadministration with colchicine, fesoterodine and solifenacin is contraindicated in subjects with varying degrees of renal or hepatic impairment, and coadministration with eliglustat is contraindicated in subjects that are poor or intermediate metabolizers of CYP2D6 and in subjects taking strong or moderate CYP2D6 inhibitors. (See PRECAUTIONS: Drug Interactions Section for specific examples.) This increase in drug concentrations caused by coadministration with itraconazole may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Specific examples are listed in PRECAUTIONS: Drug Interactions.

Itraconazole should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.

Itraconazole is contraindicated for patients who have shown hypersensitivity to itraconazole. There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing itraconazole to patients with hypersensitivity to other azoles.

WARNINGS

Hepatic Effects:

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition, and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued itraconazole use or reinstitution of treatment with itraconazole is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. (See PRECAUTIONS: Information for

Patients and ADVERSE REACTIONS.)

Cardiac Dysrhythmias:

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as cisapride, pimozide, methadone, or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Cardiac Disease:

Itraconazole capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. Itraconazole capsules should not be used for other indications in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk.

For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of itraconazole therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of itraconazole capsules, discontinue administration.

Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole intravenous infusion, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

Itraconazole has been associated with reports of congestive heart failure. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg although there were also cases reported among those receiving lower total daily doses.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of itraconazole and felodipine or nisoldipine is contraindicated.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, PRECAUTIONS: Drug Interactions, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Interaction potential:

Itraconazole has a potential for clinically important drug interactions. Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in PRECAUTIONS: Drug Interactions.

Interchangeability:

Itraconazole capsules and itraconazole oral solution should not be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. In addition, the topical effects of mucosal exposure may be different between the two formulations. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

PRECAUTIONS

General:

Itraconazole capsules should be administered after a full meal. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism).

Under fasted conditions, itraconazole absorption was decreased in the presence of decreased gastric acidity. The absorption of itraconazole may be decreased with the concomitant administration of antacids or gastric acid secretion suppressors. Studies conducted under fasted conditions demonstrated that administration with 8 ounces of a non-diet cola beverage resulted in increased absorption of itraconazole in AIDS patients with relative or absolute achlorhydria. This increase relative to the effects of a full meal is unknown. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism).

Hepatotoxicity:

Rare cases of serious hepatotoxicity have been observed with itraconazole treatment, including some cases within the first week. It is recommended that liver function monitoring be considered in all patients receiving itraconazole. Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction.

Neuropathy:

If neuropathy occurs that may be attributable to itraconazole capsules, the treatment should be discontinued.

Cystic Fibrosis:

If a cystic fibrosis patient does not respond to itraconazole capsules, consideration should be given to switching to alternative therapy. For more information concerning the use of itraconazole in cystic fibrosis patients see the prescribing information for itraconazole oral solution.

Hearing Loss:

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (See BOXED WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Information for Patients:

- The topical effects of mucosal exposure may be different between the itraconazole capsules and oral solution. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis. Itraconazole capsules should not be used interchangeably with itraconazole oral solution.
- Instruct patients to take itraconazole capsules with a full meal. Itraconazole capsules must be swallowed whole.
- Instruct patients about the signs and symptoms of congestive heart failure, and if these signs or symptoms occur during itraconazole administration, they should discontinue itraconazole and contact their healthcare provider immediately.
- Instruct patients to stop itraconazole treatment immediately and contact their healthcare provider if any signs and symptoms suggestive of liver dysfunction develop. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine, or pale stools.
- Instruct patients to contact their physician before taking any concomitant medications with itraconazole to ensure there are no potential drug interactions.
- Instruct patients that hearing loss can occur with the use of itraconazole. The hearing loss usually resolves when treatment is stopped, but can persist in some patients. Advise patients to discontinue therapy and inform their physicians if any hearing loss symptoms occur.
- Instruct patients that dizziness or blurred/double vision can sometimes occur with itraconazole. Advise patients that if they experience these events, they should not drive or use machines.

Drug Interactions:

Effect of Itraconazole on Other Drugs

Itraconazole and its major metabolite, hydroxy-itraconazole, are potent CYP3A4 inhibitors. Itraconazole is an inhibitor of the drug transporters P-glycoprotein and breast cancer resistance protein (BCRP).

Consequently, itraconazole capsules has the potential to interact with many concomitant drugs resulting in either increased or sometimes decreased concentrations of the concomitant drugs. Increased concentrations may increase the risk of adverse reactions associated with the concomitant drug which can be severe or life-threatening in some cases (e.g., QT prolongation, *Torsade de Pointes*, respiratory depression, hepatic adverse reactions, hypersensitivity reactions, myelosuppression, hypotension, seizures, angioedema, atrial fibrillation, bradycardia, priapism). Reduced concentrations of concomitant drugs may reduce their efficacy. Table 1 lists examples of drugs that may have their concentrations affected by itraconazole, but is not a comprehensive list. Refer to the approved product labeling to become familiar with the interaction pathways, risk potential, and specific actions to be taken with regards to each concomitant drug prior to initiating therapy with itraconazole.

Although many of the clinical drug interactions in Table 1 are based on information with a similar azole antifungal, ketoconazole, these interactions are expected to occur with itraconazole.

Table 1 Drug Interactions with Itraconazole that Affect Concomitant Drug Concentrations

Concomitant Drug Within Class	**Prevention or Management**
Drug Interactions with Itraconazolethat Increase Concomitant Drug Concentrations and May Increase Risk of Adverse Reactions Associated with the Concomitant Drug	
Alpha Blockers	
Alfuzosin Silodosin Tamsulosin	Not recommended during and 2 weeks after itraconazole treatment.
Analgesics	
Methadone	Contraindicated during and 2 weeks after itraconazole treatment.
Fentanyl	Not recommended during and 2 weeks after itraconazole treatment.
Alfentanil Buprenorphine (IV and sublingual) Oxycodone [a] Sufentanil	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Antiarrhythmics	
Disopyramide Dofetilide Dronedarone Quinidine [a]	Contraindicated during and 2 weeks after itraconazole treatment.
Digoxin [a]	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Antibacterials	
Bedaquiline [b]	Concomitant itraconazole not recommended for more than 2 weeks at any time during bedaquiline treatment.
Rifabutin	Not recommended 2 weeks before, during, and 2 weeks after itraconazole treatment. .See also Table 2.
Clarithromycin	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. See also Table 2.
Trimetrexate	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Anticoagulants and Antiplatelets	
Ticagrelor	Contraindicated during and 2 weeks after itraconazole treatment.
Apixaban Rivaroxaban Vorapaxar	Not recommended during and 2 weeks after itraconazole treatment.
Cilostazol Dabigatran Warfarin	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Anticonvulsants	
Carbamazepine	Not recommended 2 weeks before, during, and 2 weeks after itraconazole treatment. See also Table 2.
Antidiabetic Drugs	

Repaglinide [a] Saxagliptin	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Antihelminthics, Antifungals and Antiprotozoals	
Isavuconazonium	Contraindicated during and 2 weeks after itraconazole treatment.
Praziquantel	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Artemether-lumefantrine Quinine [a]	Monitor for adverse reactions.
Antimigraine Drugs	
Ergot alkaloids (e.g., dihydroergotamine, ergotamine)	Contraindicated during and 2 weeks after itraconazole treatment.
Eletriptan	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary
Antineoplastics	
Irinotecan	Contraindicated during and 2 weeks after itraconazole treatment.
Axitinib Bosutinib Cabazitaxel Cabozantinib Ceritinib Cobimetinib [a] Crizotinib Dabrafenib Dasatinib Docetaxel Ibrutinib Lapatinib Nilotinib Olaparib [a] Pazopanib Sunitinib Trabectedin Trastuzumab emtansine Vinca alkaloids	Not recommended during and 2 weeks after itraconazole treatment.
Bortezomib Brentuximab-vedotin Busulfan [a] Erlotinib Gefitinib [a] Idelalisib Imatinib Ixabepilone Nintedanib Panobinostat Ponatinib Ruxolitinib Sonidegib Vandetanib [a]	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For idelalisib, see also Table 2.
Antipsychotics, Anxiolytics and Hypnotics	
Alprazolam [a] Aripiprazole [a] Buspirone [a] Diazepam [a] Haloperidol [a] Midazolam (IV) [a] Quetiapine Ramelteon Risperidone [a] Suvorexant	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Zopiclone [a]	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Lurasidone Midazolam (oral) [a] Pimozide Triazolam [a]	Contraindicated during and 2 weeks after itraconazole treatment.
Antivirals	
Simeprevir	Not recommended during and 2 weeks after itraconazole treatment.
Daclatasvir Indinavir [a] Maraviroc	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For indinavir, see also Table 2.
Cobicistat Elvitegravir (ritonavir-boosted) Ritonavir Saquinavir (unboosted) [a]	Monitor for adverse reactions. See also Table 2.

Tenofovir disoproxil fumarate		Monitor for adverse reactions.
Beta Blockers		
Nadolol [a]		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Calcium Channel Blockers		
Felodipine [a] Nisoldipine		Contraindicated during and 2 weeks after itraconazole treatment.
Diltiazem Other dihydropyridines Verapamil		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For diltiazem, see also Table 2.
Cardiovascular Drugs, Miscellaneous		
Ivabradine Ranolazine		Contraindicated during and 2 weeks after itraconazole treatment.
Aliskiren [a] Riociguat Sildenafil (for pulmonary hypertension) Tadalafil (for pulmonary hypertension)		Not recommended during and 2 weeks after itraconazole treatment. For sildenafil and tadalafil, see also Urologic Drugs below.
Bosentan Guanfacine		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Contraceptives		
Dienogest Ulipristal		Monitor for adverse reactions.
Diuretics		
Eplerenone		Contraindicated during and 2 weeks after itraconazole treatment.
Gastrointestinal Drugs		
Cisapride Naloxegol		Contraindicated during and 2 weeks after itraconazole treatment.
Aprepitant Loperamide [a]		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Netupitant		Monitor for adverse reactions.
Immunosuppressants		
Everolimus Sirolimus Temsirolimus (IV)		Not recommended during and 2 weeks after itraconazole treatment.
Budesonide (inhalation) [a] Budesonide (non inhalation) Ciclesonide (inhalation) Cyclosporine (IV) [a] Cyclosporine (non- IV) Dexamethasone [a]	Fluticasone (inhalation) [a] Fluticasone (nasal) Methylprednisolone [a] Tacrolimus (IV) [a] Tacrolimus (oral)	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Lipid-Lowering Drugs		
Lomitapide Lovastatin [a] Simvastatin [a]		Contraindicated during and 2 weeks after itraconazole treatment.
Atorvastatin [a]		Monitor for drug adverse reactions. Concomitant drug dose reduction may be necessary
Respiratory Drugs		
Salmeterol		Not recommended during and 2 weeks after itraconazole treatment.
SSRIs, Tricyclics and Related Antidepressants		
Venlafaxine		Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Urologic Drugs		
Avanafil		Contraindicated during and 2 weeks after itraconazole treatment.
		Patients with moderate to severe renal or hepatic impairment: Contraindicated during and 2 weeks after

Fesoterodine	itraconazole treatment. *Other patients*: Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Solifenacin	*Patients with severe renal or moderate to severe hepatic impairment*: Contraindicated during and 2 weeks after itraconazole treatment. *Other patients*: Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Darifenacin Vardenafil	Not recommended during and 2 weeks after itraconazole treatment.
Dutasteride Oxybutynin [a] Sildenafil (for erectile dysfunction) Tadalafil (for erectile dysfunction and benign prostatic hyperplasia) Tolterodine	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary. For sildenafil and tadalafil, see also Cardiovascular Drugs above.
Miscellaneous Drugs and Other Substances	
Colchicine	*Patients with renal or hepatic impairment:* Contraindicated during and 2 weeks after itraconazole treatment. *Other patients*: Not recommended during and 2 weeks after itraconazole treatment.
Eliglustat	*CYP2D6 EMs [c] taking a strong or moderate CYP2D6 inhibitor, CYP2D6 IMs [c], or CYP2D6 PMs [c]*: Contraindicated during and 2 weeks after itraconazole treatment. *CYP2D6 EMs [c] not taking a strong or moderate CYP2D6 inhibitor* : Monitor for adverse reactions. Eliglustat dose reduction may be necessary.
Lumacaftor/Ivacaftor	Not recommended 2 weeks before, during, and 2 weeks after itraconazole treatment.
Alitretinoin (oral) Cabergoline Cannabinoids Cinacalcet Ivacaftor	Monitor for adverse reactions. Concomitant drug dose reduction may be necessary.
Vasopressin Receptor Antagonists	
Conivaptan Tolvaptan	Not recommended during and 2 weeks after itraconazole treatment.
Drug Interactions with Itraconazole that Decrease Concomitant Drug Concentrations and May Reduce Efficacy of the Concomitant Drug	
Antineoplastics	
Regorafenib	Not recommended during and 2 weeks after itraconazole treatment.
Gastrointestinal Drugs	
Saccharomyces boulardii	Not recommended during and 2 weeks after itraconazole treatment.
Nonsteroidal Anti-Inflammatory Drugs	
Meloxicam [a]	Concomitant drug dose increase may be necessary.

[a]Based on clinical drug interaction information with itraconazole.
[b]Based on 400 mg Bedaquiline once daily for 2 weeks.
[c]EMs: extensive metabolizers; IMs: intermediate metabolizers, PMs: poor metabolizers

Effect of Other Drugs on Itraconazole

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Some concomitant drugs have the potential to interact with itraconazole resulting in either increased or sometimes decreased concentrations of itraconazole. Increased concentrations may increase the risk of adverse reactions associated with itraconazole. Decreased concentrations may reduce itraconazole

efficacy.

Table 2 lists examples of drugs that may affect itraconazole concentrations, but is not a comprehensive list. Refer to the approved product labeling to become familiar with the interaction pathways, risk potential and specific actions to be taken with regards to each concomitant drug prior to initiating therapy with itraconazole.

Although many of the clinical drug interactions in Table 2 are based on information with a similar azole antifungal, ketoconazole, these interactions are expected to occur with itraconazole.

Table 2. Drug Interactions with Other Drugs that Affect Itraconazole Concentrations	
Concomitant Drug Within Class	**Prevention or Management**
Drug Interactions with Other Drugs that Increase ItraconazoleConcentrations and May Increase Risk of Adverse Reactions Associated with Itraconazole	
Antibacterials	
Ciprofloxacin * Erythromycin * Clarithromycin *	Monitor for adverse reactions. Itraconazole dose reduction may be necessary.
Antineoplastics	
Idelalisib	Monitor for adverse reactions. Itraconazole dose reduction may be necessary. See also Table 1.
Antivirals	
Cobicistat Darunavir (ritonavir-boosted) Elvitegravir (ritonavir-boosted) Fosamprenavir (ritonavir-boosted) Indinavir * Ritonavir Saquinavir	Monitor for adverse reactions. Itraconazole dose reduction may be necessary. For, cobicistat, elvitegravir, indinavir, ritonavir, and saquinavir, see also Table 1.
Calcium Channel Blockers	
Diltiazem	Monitor for adverse reactions. Itraconazole dose reduction may be necessary. See also Table 1.
Drug Interactions with Other Drugs that Decrease Itraconazole Concentrations and May Reduce Efficacy of Itraconazole	
Antibacterials	
Isoniazid Rifampicin *	Not recommended 2 weeks before and during itraconazole treatment.
Rifabutin *	Not recommended 2 weeks before, during, and 2 weeks after itraconazole treatment. See also Table 1.
Anticonvulsants	
Phenobarbital Phenytoin *	Not recommended 2 weeks before and during itraconazole treatment.
Carbamazepine	Not recommended 2 weeks before, during, and 2 weeks after itraconazole treatment. See also Table 1.
Antivirals	
Efavirenz * Nevirapine *	Not recommended 2 weeks before and during itraconazole treatment.
Gastrointestinal Drugs	
Drugs that reduce gastric acidity e.g. acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such as H_2 - receptor antagonists and proton pump inhibitors.	Use with caution. Administer acid neutralizing medicines at least 2 hours before or 2 hours after the intake of itraconazole
Miscellaneous Drugs and Other Substances	
Lumacaftor/Ivacaftor	Not recommended 2 weeks before, during,

	and 2 weeks after itraconazole treatment.

*Based on clinical drug interaction information with itraconazole.

Pediatric Population

Interaction studies have only been performed in adults.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10 times the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1 times the MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25 times the MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5 times the MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20 times the MRHD).

Pregnancy: Teratogenic effects. Pregnancy Category C:

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40 to 160 mg/kg/day (5 to 20 times the MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10 times the MRHD). Itraconazole has been shown to cross the placenta in a rat model. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. Itraconazole should be used for the treatment of systemic fungal infections in pregnancy only if the benefit outweighs the potential risk.

Itraconazole should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy. Itraconazole should not be administered to women of childbearing potential for the treatment of onychomycosis unless they are using effective measures to prevent pregnancy and they begin therapy on the second or third day following the onset of menses. Effective contraception should be continued throughout itraconazole therapy and for 2 months following the end of treatment.

During post-marketing experience, cases of congenital abnormalities have been reported. (See ADVERSE REACTIONS: Post-marketing Experience.)

Nursing Mothers:

Itraconazole is excreted in human milk; therefore, the expected benefits of itraconazole therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid potential transmission of HIV to uninfected infants.

Pediatric Use:

The efficacy and safety of itraconazole have not been established in pediatric patients.

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5 times the MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of

the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (10 times the MRHD) over 1 year or 160 mg/kg/day (20 times the MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats.

Geriatric Use:

Clinical studies of itraconazole capsules did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. It is advised to use itraconazole capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (See BOXED WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions).

HIV-Infected Patients:

Because hypochlorhydria has been reported in HIV-infected individuals, the absorption of itraconazole in these patients may be decreased.

Renal Impairment:

Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal impairment. Caution should be exercised when itraconazole is administered in this patient population and dose adjustment may be needed. (See CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

Hepatic Impairment:

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with itraconazole is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. (See CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. The risks and benefits of itraconazole use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: Hepatotoxicity and Information for Patients.)

Adverse Events in the Treatment of Systemic Fungal Infections

Adverse event data were derived from 602 patients treated for systemic fungal disease in U.S. clinical trials who were immunocompromised or receiving multiple concomitant medications. Treatment was discontinued in 10.5% of patients due to adverse events. The median duration before discontinuation of

therapy was 81 days (range: 2 to 776 days). The table lists adverse events reported by at least 1% of patients.

Table 3: Clinical Trials of Systemic Fungal Infections: Adverse Events Occurring with an Incidence of Greater than or Equal to 1%

Body System/Adverse Event	Incidence (%) (N=602)
Gastrointestinal	
Nausea	11
Vomiting	5
Diarrhea	3
Abdominal Pain	2
Anorexia	1
Body as a Whole	
Edema	4
Fatigue	3
Fever	3
Malaise	1
Skin and Appendages	
Rash *	9
Pruritus	3
Central/Peripheral Nervous System	
Headache	4
Dizziness	2
Psychiatric	
Libido Decreased	1
Somnolence	1
Cardiovascular	
Hypertension	3
Metabolic/Nutritional	
Hypokalemia	2
Urinary System	
Albuminuria	1
Liver and Biliary System	
Hepatic Function Abnormal	3
Reproductive System, Male	
Impotence	1

* Rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications.

Adverse events infrequently reported in all studies included constipation, gastritis, depression, insomnia, tinnitus, menstrual disorder, adrenal insufficiency, gynecomastia, and male breast pain.

Adverse Events Reported in Toenail Onychomycosis Clinical Trials

Patients in these trials were on a continuous dosing regimen of 200 mg once daily for 12 consecutive weeks.

The following adverse events led to temporary or permanent discontinuation of therapy.

Table 4: Clinical Trials of Onychomycosis of the Toenail: Adverse Events Leading to Temporary or Permanent Discontinuation of Therapy

Adverse Event	Incidence (%) Itraconazole (N=112)
Elevated Liver Enzymes (greater than twice the upper limit of normal)	4

Gastrointestinal Disorders	4
Rash	3
Hypertension	2
Orthostatic Hypotension	1
Headache	1
Malaise	1
Myalgia	1
Vasculitis	1
Vertigo	1

The following adverse events occurred with an incidence of greater than or equal to 1% (N=112): headache: 10%; rhinitis: 9%; upper respiratory tract infection: 8%; sinusitis, injury: 7%; diarrhea, dyspepsia, flatulence, abdominal pain, dizziness, rash: 4%; cystitis, urinary tract infection, liver function abnormality, myalgia, nausea: 3%; appetite increased, constipation, gastritis, gastroenteritis, pharyngitis, asthenia, fever, pain, tremor, herpes zoster, abnormal dreaming: 2%.

Adverse Events Reported in Fingernail Onychomycosis Clinical Trials

Patients in these trials were on a pulse regimen consisting of two 1-week treatment periods of 200 mg twice daily, separated by a 3-week period without drug.

The following adverse events led to temporary or permanent discontinuation of therapy.

Table 5: Clinical Trials of Onychomycosis of the Fingernail: Adverse Events Leading to Temporary or Permanent Discontinuation of Therapy

Adverse Event	**Incidence (%) Itraconazole (N=37)**
Rash/Pruritus	3
Hypertriglyceridemia	3

The following adverse events occurred with an incidence of greater than or equal to 1% (N=37): headache: 8%; pruritus, nausea, rhinitis: 5%; rash, bursitis, anxiety, depression, constipation, abdominal pain, dyspepsia, ulcerative stomatitis, gingivitis, hypertriglyceridemia, sinusitis, fatigue, malaise, pain, injury: 3%.

Adverse Events Reported from Other Clinical Trials

In addition, the following adverse drug reaction was reported in patients who participated in itraconazole capsules clinical trials: *Hepatobiliary Disorders:* hyperbilirubinemia.

The following is a list of additional adverse drug reactions associated with itraconazole that have been reported in clinical trials of itraconazole oral solution and itraconazole IV excluding the adverse reaction term "Injection site inflammation" which is specific to the injection route of administration:

Cardiac Disorders: cardiac failure, left ventricular failure, tachycardia;

General Disorders and Administration Site Conditions: face edema, chest pain, chills;

Hepatobiliary Disorders: hepatic failure, jaundice;

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood urea increased, gamma-glutamyltransferase increased, urine analysis abnormal;

Metabolism and Nutrition Disorders: hyperglycemia, hyperkalemia, hypomagnesemia;

Psychiatric Disorders: confusional state;

Renal and Urinary Disorders: renal impairment;

Respiratory, Thoracic and Mediastinal Disorders: dysphonia, cough;

Skin and Subcutaneous Tissue Disorders: rash erythematous, hyperhidrosis;

Vascular Disorders: hypotension

Post-marketing Experience

Adverse drug reactions that have been first identified during post-marketing experience with itraconazole (all formulations) are listed in the table below. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 6: Postmarketing Reports of Adverse Drug Reactions

Blood and Lymphatic System Disorders:	Leukopenia, neutropenia, thrombocytopenia
Immune System Disorders:	Anaphylaxis; anaphylactic, anaphylactoid and allergic reactions; serum sickness; angioneurotic edema
Nervous System Disorders:	Peripheral neuropathy, paresthesia, hypoesthesia, tremor
Eye Disorders:	Visual disturbances, including vision blurred and diplopia
Ear and Labyrinth Disorders:	Transient or permanent hearing loss
Cardiac Disorders:	Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders:	Pulmonary edema, dyspnea
Gastrointestinal Disorders:	Pancreatitis, dysgeusia
Hepatobiliary Disorders:	Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis
Skin and Subcutaneous Tissue Disorders:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, alopecia, photosensitivity, urticaria
Musculoskeletal and Connective Tissue Disorders:	Arthralgia
Renal and Urinary Disorders:	Urinary incontinence, pollakiuria
Reproductive System and Breast Disorders:	Erectile dysfunction
General Disorders and Administration Site Conditions:	Peripheral edema
Investigations:	Blood creatine phosphokinase increased

There is limited information on the use of itraconazole during pregnancy. Cases of congenital abnormalities including skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations have been reported during post-marketing experience. A causal relationship with itraconazole has not been established. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

OVERDOSAGE

Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures should be employed. Activated charcoal may be given if considered appropriate. In general, adverse events reported with overdose have been consistent with adverse drug reactions already listed in this package insert for itraconazole. (See ADVERSE REACTIONS.)

DOSAGE AND ADMINISTRATION

Itraconazole capsules should be taken with a full meal to ensure maximal absorption. Itraconazole capsules must be swallowed whole.

Itraconazole capsules are a different preparation than itraconazole oral solution and should not be used interchangeably.

Treatment of Blastomycosis and Histoplasmosis:

The recommended dose is 200 mg once daily (2 capsules). If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 100-mg increments to a maximum of 400 mg daily. Doses above 200 mg/day should be given in two divided doses.

Treatment of Aspergillosis:

A daily dose of 200 to 400 mg is recommended.

Treatment in Life-Threatening Situations:

In life-threatening situations, a loading dose should be used.

Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose of 200 mg (2 capsules) three times daily (600 mg/day) be given for the first 3 days of treatment.

Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Itraconazole capsules and itraconazole oral solution should not be used interchangeably. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

Treatment of Onychomycosis:

Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) once daily for 12 consecutive weeks.

Treatment of Onychomycosis:

Fingernails only: The recommended dosing regimen is 2 treatment pulses, each consisting of 200 mg (2 capsules) b.i.d. (400 mg/day) for 1 week. The pulses are separated by a 3-week period without itraconazole.

Use in Patients with Renal Impairment:

Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations and PRECAUTIONS.)

Use in Patients with Hepatic Impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and PRECAUTIONS.)

HOW SUPPLIED

Itraconazole capsules are available containing 100 mg of itraconazole, with a pink transparent body printed 100 and blue cap printed AI, size ‘0’, hard gelatin capsules containing white to off-white pellets. The capsules are supplied in unit-dose blister packs of 3 × 10 capsules (NDC 16729-271-51), bottles of 30 capsules (NDC 16729-271-10), bottles of 500 capsules (NDC 16729-271-16) and in the DosingPak containing 7 blister packs × 4 capsules each (NDC 16729-271-72).

Store at controlled room temperature 15°C to 25°C (59° F to 77°F). Protect from light and moisture.

Keep out of reach of children.

Manufactured For:

Accord Healthcare, Inc.,
1009, Slater Road,
Suite 210-B,
Durham, NC 27703,
USA

Manufactured By:

Intas Pharmaceuticals Limited
Plot No. : 457, 458,
Village – Matoda,
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10 2089 1 680095

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PATIENT INFORMATION

Itraconazole Capsules

(IT-ra-KON-a-zole)

This summary contains important information about itraconazole capsules. This information is for patients who have been prescribed itraconazole capsules to treat fungal nail infections **. If your doctor prescribed itraconazole capsules for medical problems other than fungal nail infections, ask your doctor if there is any information in this summary that does not apply to you.** Read this information carefully each time you start to use itraconazole capsules. This information does not take the place of discussion between you and your doctor. Only your doctor can decide if itraconazole capsules are the right treatment for you. If you do not understand some of this information or have any questions, talk with your doctor or pharmacist.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT ITRACONAZOLE CAPSULES?

Itraconazole capsules are used to treat fungal nail infections. However, itraconazole capsules are not for everyone. **Do not take itraconazole capsules for fungal nail infections if you have had heart failure, including congestive heart failure. You should not take itraconazole capsules if you are taking certain medicines that could lead to serious or life-threatening medical problems.** (See " Who Should Not Take Itraconazole Capsules?" below.)

If you have had heart, lung, liver, kidney or other serious health problems, ask your doctor if it is safe for you to take itraconazole capsules.

WHAT HAPPENS IF I HAVE A FUNGAL NAIL INFECTION?

Anyone can have a fungal nail infection, but it is usually found in adults. When a fungus infects the tip or sides of a nail, the infected part of the nail may turn yellow or brown. If not treated, the fungus may spread under the nail towards the cuticle. If the fungus spreads, more of the nail may change color, may become thick or brittle, and the tip of the nail may become raised. In some patients, this can cause pain and discomfort.

WHAT ARE ITRACONAZOLE CAPSULES?

Itraconazole capsules are a prescription medicine used to treat fungal infections of the toenails and fingernails. It is also used to treat some types of fungal infections in other areas of your body. We do not know if itraconazole capsules works in children with fungal nail infections or if it is safe for children to take.

Itraconazole comes in the form of capsules and liquid (oral solution). The capsule and liquid forms work differently, so you should not use one in place of the other. This Patient Information discusses only the capsule form of itraconazole. You will get these capsules in a medicine bottle or a itraconazole capsules DosingPak. The DosingPak contains 28 capsules for treatment of your fungal nail infection.

Itraconazole goes into your bloodstream and travels to the source of the infection underneath the nail so that it can fight the infection there. Improved nails may not be obvious for several months after the treatment period is finished because it usually takes about 6 months to grow a new fingernail and 12 months to grow a new toenail.

WHO SHOULD NOT TAKE ITRACONAZOLE CAPSULES?

Itraconazole capsules are not for everyone. Your doctor will decide if itraconazole capsules are the right treatment for you. **Some patients should not take itraconazole capsules because they may have certain health problems or may be taking certain medicines that could lead to serious or life-threatening medical problems.**

Tell your doctor and pharmacist the name of all the prescription and non-prescription medicines you are taking, including dietary supplements and herbal remedies. Also tell your doctor about any other medical conditions you have had, especially heart, lung, liver or kidney conditions; or if you have cystic fibrosis, or have had an allergic reaction to itraconazole capsules or any other antifungal medicines.

Never take Itraconazole capsules if you:

- have had heart failure, including congestive heart failure.
- are taking any of the medicines listed below. Dangerous or even life-threatening side effects could result:
  - avanafil (such as Stendra™)
  - cisapride (such as Propulsid ®)
  - colchicine (such as Colcrys™) [if you also have pre-existing kidney or liver impairment]
  - disopyramide (such as Norpace ®)
  - dofetilide (such as Tikosyn™)
  - dronedarone (such as Multaq ®)
  - eliglustat (such as Cerdelga ™) [if you know you do not break down drugs that are broken down by the enzyme CYP 2D6]
  - eplerenone (such as Inspra ®)
  - ergot alkaloids (such as Migranal ®, Ergonovine, Cafergot ®, Methergine ®)
  - felodipine (such as Plendil ®)
  - fesoterodine (such as Toviaz ®) [if you also have pre-existing kidney or liver impairment]
  - irinotecan (such as Camptosar ®)
  - isavuconazole (such as Cresemba ®)
  - ivabradine (such as Corlanor ®)
  - lomitapide (such as Juxtapid ™)
  - lovastatin (such as Mevacor ®, Advicor ®, Altocor™)
  - lurasidone (such as Latuda ®)
  - methadone (such as Dolophine ®)
  - midazolam (such as Versed ®)
  - naloxegol (such as Movantik ®)
  - nisoldipine (such as Sular ®)
  - pimozide (such as Orap ®)
  - quinidine (such as Cardioquin ®, Quinaglute ®, Quinidex ®)
  - ranolazine (such as Ranexa ®)
  - simvastatin (such as Zocor ®)
  - solifenacin (such as Vesicare ®) [if you also have pre-existing kidney or liver impairment]
  - ticagrelor (such as Brilinta ®)
  - triazolam (such as Hacion ®)
- have ever had an allergic reaction to itraconazole.

Taking itraconazole capsules with certain other medicines may lead to serious or life-threatening medical problems. Tell your doctor and pharmacist the name of all the prescription and non-prescription medicines you are taking, including dietary supplements and herbal remedies. Your doctor will decide if itraconazole capsules is the right treatment for you.

WHAT SHOULD I KNOW ABOUT ITRACONAZOLE CAPSULES AND PREGNANCY OR BREAST FEEDING?

Never take itraconazole capsules if you have a fungal nail infection and are pregnant or planning to become pregnant within 2 months after you have finished your treatment.

If you are able to become pregnant, you should use effective birth control during itraconazole capsules treatment and for 2 months after finishing treatment. Ask your doctor about effective types of birth control.

If you are breast-feeding, talk with your doctor about whether you should take itraconazole capsules.

HOW SHOULD I TAKE ITRACONAZOLE CAPSULES?

Always take itraconazole capsules during or right after a full meal.

Your doctor will decide the right dose for you. Depending on your infection, you will take itraconazole capsules once a day for 12 weeks, or twice a day for 1 week in a "pulse" dosing schedule. You will receive either a bottle of capsules or a DosingPak. Do not skip any doses. Be sure to finish all your itraconazole capsules as prescribed by your doctor.

If you have ever had liver problems, your doctor should do a blood test to check your condition. If you haven't had liver problems, your doctor may recommend blood tests to check the condition of your liver because patients taking itraconazole capsules can develop liver problems.

Itraconazole capsules can sometimes cause dizziness or blurred/double vision. If you have these symptoms, do not drive or use machines.

If you forget to take or miss doses of itraconazole capsules, ask your doctor what you should do with the missed doses.

Itraconazole Capsules 100 mg DosingPak

If you use the DosingPak, you will take itraconazole capsules 100 mg for 1 week and then take no itraconazole capsules 100 mg for the next 3 weeks before repeating the 1-week treatment. This is called "pulse dosing." Itraconazole capsules 100 mg DosingPak contains enough medicine for one "pulse" (1 week of treatment).

Itraconazole capsules 100 mg DosingPak comes with special instructions. It contains 7 blisters-one for each day of treatment. Inside each blister containing 4 capsules.

- Take 2 capsules in the morning and 2 capsules in the evening. This means you will take 4 capsules a day for 7 days. At the end of 7 days, you will have taken all of the capsules in the DosingPak box.
- After you finish the DosingPak, do not take any itraconazole capsules for the next 3 weeks. Even though you are not taking any capsules during this time, itraconazole capsules keeps working inside your nails to help fight the fungal infection.
- You will need more than one "pulse" to treat your fungal nail infection. When your doctor prescribes another pulse treatment, be sure to get your refill before the end of week 4.

<table>
<tr><th colspan="15">Itraconazole Capsules Pulse Dosing</th></tr>
<tr><th colspan="15">Take 2 itraconazole capsules 100 mg twice a day for 1 week</th></tr>
<tr><th></th><th colspan="2">Day 1</th><th colspan="2">Day 2</th><th colspan="2">Day 3</th><th colspan="2">Day 4</th><th colspan="2">Day 5</th><th colspan="2">Day 6</th><th colspan="2">Day 7</th></tr>
<tr><th></th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th><th>AM</th><th>PM</th></tr>
<tr><td>Week 1</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td><td>//</td></tr>
<tr><td>Week 2</td><td colspan="14" rowspan="3">For the next 3 weeks, do not take any itraconazole capsules.
Remember to get a refill before the end of Week 4
when your doctor prescribes another DosingPak.</td></tr>
<tr><td>Week 3</td></tr>
<tr><td>Week 4</td></tr>
</table>

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ITRACONAZOLE CAPSULES?

The most common side effects include: headache, and digestive system problems (such as nausea, and abdominal pain).

Stop itraconazole capsules and call your doctor or get medical assistance right away if you have a severe allergic reaction. Symptoms of an allergic reaction may include skin rash, itching, hives, shortness of breath or difficulty breathing, and/or swelling of the face. Very rarely, an oversensitivity to sunlight, a tingling sensation in the limbs or a severe skin disorder can occur. If any of these symptoms occur, stop taking itraconazole capsules and contact your doctor.

Stop itraconazole capsules and call your doctor right away if you develop shortness of breath; have unusual swelling of your feet, ankles or legs; suddenly gain weight; are unusually tired; cough up white or pink phlegm; have unusual fast heartbeats; or begin to wake up at night. In rare cases, patients taking itraconazole capsules could develop serious heart problems, and these could be warning signs of heart failure.

Stop itraconazole capsules and call your doctor right away if you become unusually tired; lose your appetite; or develop nausea, abdominal pain, or vomiting, a yellow color to your skin or eyes, or dark colored urine or pale stools (bowel movements). In rare cases, patients taking itraconazole could develop serious liver problems and these could be warning signs.

Stop itraconazole capsules and call your doctor right away if you experience any hearing loss symptoms. In very rare cases, patients taking itraconazole capsules have reported temporary or permanent hearing loss.

Call your doctor right away if you develop tingling or numbness in your extremities (hands or feet), if your vision gets blurry or you see double, if you hear a ringing in your ears, if you lose the ability to control your urine or urinate much more than usual.

Additional possible side effects include upset stomach, vomiting, constipation, fever, inflammation of the pancreas, menstrual disorder, erectile dysfunction, dizziness, muscle pain, painful joints, unpleasant taste, or hair loss. These are not all the side effects of itraconazole capsules. Your doctor or pharmacist can give you a more complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

WHAT SHOULD I DO IF I TAKE AN OVERDOSE OF ITRACONAZOLE CAPSULES?

If you think you took too much itraconazole capsules, call your doctor or local poison control center, or go to the nearest hospital emergency room right away.

HOW SHOULD I STORE ITRACONAZOLE CAPSULES?

Keep all medicines, including itraconazole capsules, out of the reach of children.

Store itraconazole capsules and the DosingPak at room temperature in a dry place away from light.

GENERAL ADVICE ABOUT ITRACONAZOLE CAPSULES

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use itraconazole capsules for a condition for which it was not prescribed. Do not give itraconazole to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about itraconazole. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about itraconazole capsules that is written for health professionals or go to www.accordhealthcare.us or call Accord Healthcare Inc. at 1-866-941-7875.

This patient information has been approved by the U.S. Food and Drug Administration.

Manufactured For:

Accord Healthcare, Inc.,
1009, Slater Road,
Suite 210-B,
Durham, NC 27703,
USA

Manufactured By:

Intas Pharmaceuticals Limited,
Plot No. : 457, 458,
Village – Matoda,
Bavla Road, Ta.- Sanand,
Dist.- Ahmedabad – 382 210.
India.

10 2089 1 680095

Issued December 2017

PRINCIPAL DISPLAY PANEL - Itraconazole 100 mg capsules

NDC 16729- **271**-16

Itraconazole
Capsules

100 mg

Rx only

PHARMACIST: Dispense the enclosed Patient Information Leaflet to each patient.

500 Capsules

Itraconazole 100 mg capsules

NDC 16729- **271**-72 **DosingPak**

Itraconazole
Capsules

100 mg Rx only 7 days of treatment
Product information

PHARMACIST: Dispense the enclosed Patient Information Leaflet to each patient.

Contains 7 blisters x 4 capsules each

Itraconazole 100 mg capsules

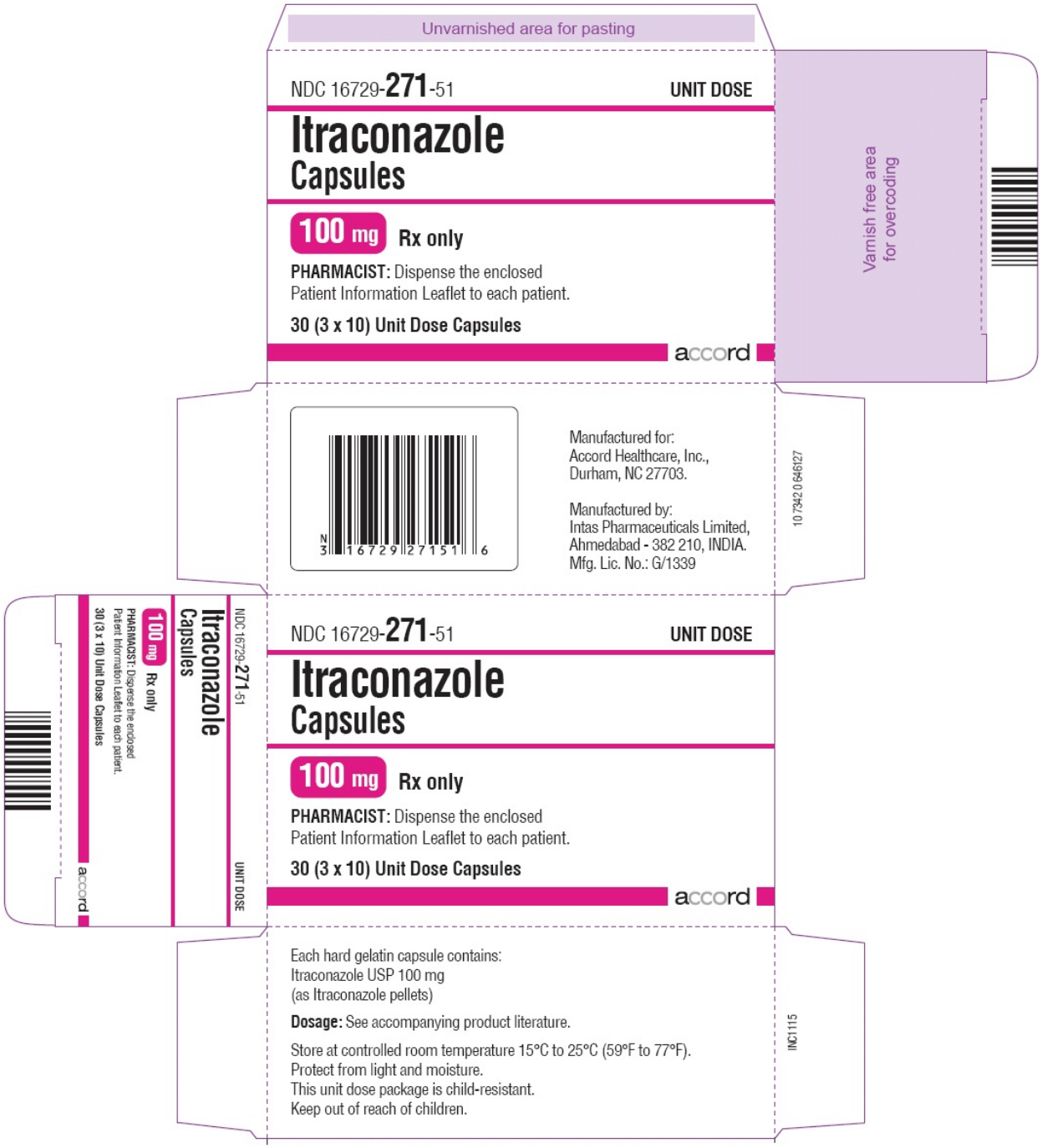
NDC 16729- **271**-51 **UNIT DOSE**

Itraconazole
Capsules

100 mg Rx only

PHARMACIST: Dispense the enclosed Patient Information Leaflet to each patient.

30 (3x10) Unit Dose Capsules



ITRACONAZOLE

itraconazole capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16729-271
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ITRACONAZOLE (UNII: 304NUG5GF4) (ITRACONAZOLE - UNII:304NUG5GF4)	ITRACONAZOLE	100 mg

Inactive Ingredients	
Ingredient Name	Strength
HYPROMELLOSE 2910 (5 MPA.S) (UNII: R75537T0T4)	
POLYETHYLENE GLYCOL 20000 (UNII: 5WKN5KL2O8)	
TALC (UNII: 7SEV7J4R1U)	
STARCH, CORN (UNII: O8232NY3SJ)	
SUCROSE (UNII: C151H8M554)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
GELATIN (UNII: 2G86QN327L)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics			
Color	pink (pink transparent) , blue	**Score**	no score
Shape	CAPSULE	**Size**	21mm
Flavor		**Imprint Code**	AI;100
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16729-271-51	3 in 1 CARTON	01/01/2024	
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:16729-271-10	30 in 1 BOTTLE; Type 0: Not a Combination Product	05/30/2017	
3	NDC:16729-271-72	7 in 1 DOSE PACK	01/01/2024	
3		4 in 1 BLISTER PACK; Type 0: Not a Combination Product		
4	NDC:16729-271-16	500 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205991	05/30/2017	

Labeler - Accord Healthcare Inc. (604222237)

Registrant - Accord Healthcare Inc. (604222237)

Establishment

Name	Address	ID/FEI	Business Operations
Intas Pharmaceuticals Ltd		725927649	manufacture(16729-271) , analysis(16729-271)

Revised: 10/2019 Accord Healthcare Inc.